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ROLE OF HORMESIS IN LIFE EXTENSION BY CALORIC RESTRICTION

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□ Caloric restriction (CR) markedly extends the life of rats, mice and several other species, and it also modulates age-associated physiological deterioration and delays the occurrence and/or slows progression of age-associated diseases. The level of CR that retards the aging processes is a low-intensity stressor, which enhances the ability of rats and mice of all ages to cope with intense stressors. CR thus exhibits a hormetic action in these species, and therefore it is hypothesized that hormesis plays a role in the life-extending and anti-aging actions of CR. Both the findings in support of this hypothesis and those opposing it are critically considered. However, it is likely that hormesis is not the only process contributing to CR-induced life extension. It is proposed that two general processes are involved in CR-induced life extension. One is the reduced endogenous generation of damaging agents, such as reactive oxygen species. The second is hormesis, which enhances processes that protect against the action of damaging agents and also promotes processes that repair the damage once it occurs.

Keywords: Aging; Low-Intensity Stressor; Damage Protection; Damage Repair.

OVERVIEW OF CALORIC RESTRICTION AND AGING

That restricting food intake can extend the life of rats was first clearly shown in the 1930s (McCay et al, 1935). This finding has been confirmed many times. For example, in a study carried out in our laboratory on male F344 rats (Masoro et al, 1989), a 40% reduction in food intake was found to increase the median length of life from 730 days for the *ad libitum*-fed rats to 936 days for the food-restricted rats ($P < 0.001$); the maximal length of life (i.e., age of the tenth percentile survivors) increased from 857 days to 1121 days ($P < 0.001$). Restricting food intake has also been found to extend the life of mice, hamster, dogs (Labrador Retrievers), fish, several invertebrate animal species (flies, nematodes, rotifers, water fleas and spiders), protozoa and yeast (Masoro, 2002).

It has long been known that the age-specific mortality rate of humans increases exponentially with increasing adult age (Gompertz, 1825). This phenomenon also occurs in other animal species, and the rate of this increase has been used as a measure of the rate of aging of animal populations (Finch, 1990). Indeed, several rat studies have shown that food-restriction decreases the rate of the age-associated exponential increase

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in mortality; based on this finding, the conclusion was drawn that food restriction extends life by slowing the rate of aging (Sacher, 1977; Holehan and Merry, 1986; Pletcher et al, 2000). Although life-extending food restriction has also been found to slow the age-associated increase in mortality rate in some mouse studies, in other mouse studies, the age-associated increase in mortality rate was delayed but not slowed when once underway (Masoro, 2006). Moreover, the latter finding has also been observed with *Drosophila melanogaster* (Mair et al, 2003). The classic interpretation of the *Drosophila* mortality findings and those of mice exhibiting a similar pattern is that food restriction delays the start of aging, but does not slow the rate of aging once underway. However, interpreting mortality findings in this way has recently been challenged (Driver, 2003). In my opinion, either slowing of the age-associated increase in mortality rate or delaying its occurrence is evidence that the aging processes have been retarded; in all food restriction studies in which life extension has occurred and mortality rate has been measured, one of these two scenarios has been observed.

At advanced ages, many physiological characteristics of rodents on a long-term food restriction regimen exhibit a more youthful state than in animals fed *ad libitum* (Masoro, 2002). Two different pathways are involved. In one pathway, food restriction does not initially affect the physiological characteristics but does slow the age-associated change; the slowing of the age-associated increase of serum cholesterol in rats is an example (Liepa et al, 1980). In the other pathway, food restriction almost immediately alters the physiological characteristics, but after that does not affect the rate of age-associated change. For example, food restriction in rats immediately increases the rate but does not affect the age-associated slowing of hepatic protein biosynthesis; as a result, the rate of this biosynthetic process in old food-restricted rats is closer to that of young *ad libitum*-fed rats than is the case for old *ad libitum*-fed rats (Ward, 1988).

Food restriction delays the occurrence and/or the progression of age-associated diseases (Weindruch and Walford, 1988). For example, in male F344 rats, at the time of spontaneous death, 68% of *ad libitum*-fed rats had severe nephropathy and 19% severe cardiomyopathy, compared to 1% and 6% respectively of food-restricted rats—even though the latter die at a much older age (Maeda et al, 1985). Food restriction was found to delay the onset of leukemia/lymphoma, a major neoplastic disease in this rat strain, but not to slow the progression of this cancer (Shimokawa et al, 1993).

There is a substantial body of evidence in support of the view that a decrease in caloric intake is the dietary factor responsible for the life-prolonging and anti-aging actions of food restriction (Masoro, 2002). Indeed, the term caloric restriction (CR) is commonly used when referring to these actions of food restriction. However, the use of CR has been

recently challenged and the suggestion made that it be replaced by the vague term, dietary restriction (DR). This challenge appears to relate to the finding in rats that an 80% restriction in dietary methionine content results in life extension similar in magnitude to that of a 40% reduction in food intake (Zimmerman et al, 2003). Similar findings were reported for mice (Miller et al, 2005). These findings have led to speculation that a reduction in dietary protein intake rather than caloric intake is the dietary factor responsible for life extension. This speculation ignores the finding that a reduction in food intake by 40% without reducing protein intake is as effective in extending life as reducing the intake of food including protein by 40% (Masoro et al 1989). Clearly, there is no need to reduce the intake of protein for food restriction to extend the life of rats. Thus, based on current findings, there is no need to replace CR with the vague term DR.

Of course, the question that is always asked when first hearing about the remarkable effect of CR on the longevity of animal species is whether it has a similar effect in humans. No one knows the answer nor is it likely that it will ever be possible to definitively answer this question. Indeed, this question was asked of the leading CR researchers, half of whom felt CR would extend human life span and half felt it would not (LeBourg and Rattan, 2006); strikingly whichever the answer given, reason for the answer differed among the experts.

Many hypotheses have been proposed for the biological mechanism underlying the life-extending and anti-aging actions of CR. Each hypothesis is based on one of CR's many physiological actions, such as slowing growth, reducing body fat, altering apoptosis, decreasing body temperature and increasing physical activity, as well as the attenuation of oxidative damage and reduction in glycemia and insulinemia. Although these as well as other actions may well play a role, a unifying hypothesis is needed. The concept of hormesis may well provide such a hypothesis, at least for part of the anti-aging action of CR.

CONCEPT OF HORMESIS IN THE CONTEXT OF AGING

Classically, hormesis refers to phenomena in which the response of an organism to a chemical or physical agent is qualitatively different when the agent is of high intensity than when it is of low intensity. An example would be a toxic chemical agent exhibiting favorable effects when present in the low concentration range; i.e., the relationship between the concentration of this agent and beneficial versus unfavorable effects is quantitatively described by a j-shaped or inverted j-shaped curve.

Suresh Rattan has modified this classic view when using hormesis in the gerontologic context. He defines it in relation to aging as follows: *Hormesis in aging refers to beneficial effects resulting from the cellular responses to*

mild, repeated stress (Rattan, 2001). He further proposes that as an aging retardant, hormesis is based on the principle that repeated exposure to mild stress stimulates maintenance and repair processes (Rattan, 2004). It is Rattan's views that serve as the basis for my consideration of the role of hormesis in the life-extending and anti-aging actions of CR.

CR: A LONG-TERM, REPEATED, LOW-INTENSITY STRESSOR

In young rodents, CR causes a daily increase in the afternoon peak concentration of plasma corticosterone, the major glucocorticoid in these species (Sabatino et al, 1991; Klebanov et al, 1995). Although this elevation disappears with increasing age, further investigation reveals that plasma free corticosterone exhibits this daily elevation throughout life because of an age-associated decrease in the plasma concentration of corticoid-binding globulin (Sabatino et al, 1991). It is the level of the free hormone that underlies the physiological actions of this hormone (Mendel, 1989). This daily elevation of plasma corticosterone indicates that CR causes a daily period of stress in these rodent species (Munck et al, 1984). Moreover, the CR-induced daily elevation of plasma free corticosterone is small compared to a stressor such as restraint, which causes a rapid, marked elevation of plasma corticosterone (Sabatino et al, 1991). Thus, it can be concluded that CR is, indeed, a daily low-intensity stressor.

CR: ITS HORMETIC ACTIONS

CR protects rats and mice of all ages from the damaging action of many harmful agents (intense stressors). For example, it decreases the loss of weight that occurs in rats that have experienced surgical stress (Masoro, 1998). Rats on a CR regimen are better able to survive severe heat stress than those fed *ad libitum* (Heydari et al, 1993). In a mouse study, CR was found to decrease the irritant-induced inflammatory response (Klebanov et al, 1995). Several studies have shown that CR protects rodents from damage caused by toxic chemical agents (Berg et al, 1994; Duffy et al, 1995; Keenan et al, 1997).

Thus, CR meets the classic criteria of hormesis. A marked reduction of food intake is clearly harmful to the point of being lethal, but a long-term moderate reduction of food intake enables the organism to more successfully cope with severely damaging environments.

RELATION OF CR-INDUCED HORMESIS TO CR'S LIFE-EXTENDING AND ANTI-AGING ACTIONS

Aging (senescence) occurs because of the long-term damaging actions of both endogenous agents (e.g., those generated by the oxidative processes involved in fuel use) and exogenous agents (e.g., environmental substances that cause inflammation). Most of this damage is either

prevented by the organism's protective processes or removed by repair processes. However, as proposed in the Disposable Soma Theory of Aging, evolution selects for less energy use for maintenance of an organism than is needed for indefinite survival; how much less is a function of the hazard level of the evolutionary environment (Kirkwood, 1977). As a consequence, the rate of aging varies markedly among species, with the extent of the imbalance favoring damaging processes over protective and repair processes.

This indicates an involvement of the hormetic actions of CR in the retardation of aging and the extension of life. Indeed, several other lines of evidence support this view. For example, other moderate stressors have been associated with life extension in invertebrate species. Several different moderate intensity stressors, including heat stress, have been reported to extend the life of nematodes (Lithgow et al, 1995; Cypser and Johnson, 2002). The life of fruit flies is extended by moderate intensity heat stress and by moderate hypergravity stress (Maynard Smith, 1958; Khazaeli et al, 1997, Le Bourg et al, 2000, Hercus et al, 2003). Moderate heat stress and osmotic stress increase the replicative life span of the yeast species, *Saccharomyces cervisiae* (Shama et al, 1998; Anderson et al, 2003).

Genetic studies also link longevity to the ability of organisms to cope with harmful agents. Such a relationship has been clearly shown for single gene mutations of *D. melanogaster* (Lin et al, 1998), *C. elegans* (Lithgow and Walker, 2002), and yeast (Fabrizio et al, 2001).

In summary, a wealth of evidence supports the view that an increased ability to cope with damage enhances longevity, probably by retarding damage from aging processes. Thus, it is likely that the hormetic actions of CR play a major role in its life-extending and anti-aging actions.

CR'S HORMETIC PATHWAY

The pathway by which CR enhances protective and repair processes has not yet been delineated. However, some progress may have been made in regard to the CR-induced increase in the replicative life span of *S. cervisiae*. The Guarente laboratory reported that a functional *SIR2* gene is required for CR to increase replicative longevity in this yeast species (Lin et al, 2000). Subsequently, the Sinclair laboratory reported that CR did so by increasing the level of a nicotinamidase (pnc), thereby decreasing the concentration of nicotinamide, an inhibitor of the sir2 protein deacetylase activity (Anderson et al, 2003). They also found that two other moderate stressors (osmotic and heat), which increase the replicative longevity of this yeast species, also increase the sir2 protein deacetylase activity by the same mechanism. Thus, it appeared that the hormetic pathway by which CR and other moderate stressors increase sir2 deacetylase activity had been defined; what remained to be described was the pathway linking the increased sir2 deacetylase activity to the enhance-

ment of protective and repair processes. However, recent findings have cast doubt on the general biological importance of this pathway even for yeast. It has been reported that sir2 acts to decrease rather than increase the chronological life of yeast (Fabrizio et al, 2005), and that genes in nutrient-sensing pathways other than *SIR2* underlie replicative life extension in yeast (Kaeberlein et al, 2005).

Moderate stress turns on certain genes, the so-called stress-response genes (Papaconstantinou et al, 1996). Some of these genes protect against cellular damage, and thus may well be components of the hormesis pathway. Indeed, it appears that CR enhances the transcription of the *HSP70* gene by altering the HSF1 transcription factor so as to enhance its ability to bind to its DNA binding site (Heydari et al, 2000). Thus, components of possible protective hormesis pathways appear to be emerging.

In addition to increasing protection, hormesis may also activate repair processes. For example, enhancement of DNA repair processes and of the rate of protein turnover may well be components of the CR-induced hormesis pathway (Lewis et al, 1985; Guo et al, 1998).

As mentioned above, the daily peak concentration of plasma free corticosterone is significantly elevated in rats and mice on CR regimen. It is well known that glucocorticoids are needed for mammalian organisms to cope with harmful environments (Munck et al, 1984). Thus, this daily elevation of the peak concentration of plasma free corticosterone may play an important role in the life-extending and anti-aging actions of CR in rodents. The finding that the cancer-prevention action of CR in rodents is abolished by adrenalectomy gives credence to this possibility (Schwartz and Pashko, 1994). Thus, it appears that elevated glucocorticoids may be an important component of CR-induced hormesis (Schwartz and Pashko, 1994).

FINDINGS NOT IN ACCORD WITH THE HORMESIS HYPOTHESIS

It was initially concluded that hormesis is not involved in the life-extending and anti-aging actions of CR because hormetic agents known to induce increased longevity were found to affect the temporal pattern of the age-associated change in mortality rate differently than CR (Neafsey, 1990). Specifically, she pointed out that hormetic-induced increases in longevity involved an almost immediate decrease in mortality rate but no change in the age-associated increase in mortality rate in contrast to CR, which had no immediate effect on mortality rate but slowed the age-associated increase in mortality rate. However, recent studies show that the effect of CR on the temporal pattern of the age-change in mortality differs among species, strains of species and even among different populations of the same species and strain (Masoro, 2006). Indeed, Mair et al (2003) reported that initiating CR in adult *Drosophila melanogaster* results in an increase in longevity and a change in the mortality rate pattern identical

to that described by Neafsey for hormetic-induced increases in longevity. Thus, the temporal pattern of the age-associated change in mortality rate cannot be used to either support or rule out a role for hormesis in CR's life-prolonging and anti-aging actions.

Since the hormesis hypothesis proposes that CR affects its longevity and anti-aging actions by enhancing protective and repair processes, it is reasoned that CR should enable the organism to better cope with all stressors. Thus, the finding that CR fails to increase the ability to cope with some stressors is viewed as evidence against this hypothesis. However, this view fails to take into consideration the possibility that to cope with a particular stressor, there are requirements, in addition to hormesis, that must be met, and the failure to meet such requirements may mask the hormetic effect of CR. For example, rodents on a CR regimen are less able to heal skin wounds (Harrison and Archer, 1987). However, if old mice that have been on CR for most of life are allowed to eat *ad libitum* for four weeks prior to wounding, their skin wounds heal more rapidly than those of mice fed *ad libitum* throughout life (Reed et al, 1996). Wound healing requires an abundant supply of energy for cell proliferation and for the synthesis of collagen and other extracellular matrix components. Rodents on CR have a markedly reduced body fat content per unit body weight (Bertrand et al, 1980). Thus, it is likely that the limited intake and storage of energy by mice on a CR regimen mask the hormetic action of CR, which becomes manifest by a relatively brief period of *ad libitum*-feeding.

CR has also been found to decrease the ability of rats to cope with low environmental temperatures (Campbell and Richardson, 1988). Rodents meet this environmental challenge primarily by increasing heat production, and this requires an abundance of energy from dietary and stored sources. Thus, it is likely that this is another case in which a reduced supply of energy masks the hormetic action of CR; however, empirical evidence in support of this view is needed.

The effect of CR on immune function is controversial with some reports indicating that it enhances (Effros et al, 1991) and other reports indicating just the opposite (Gardner, 2005). Again, other factors may mask the hormetic effect of CR. For instance, CR slows the development of the immune system and, as a result, CR was found to decrease immune function in young mice and enhance it in old mice (Gerbase-Delima et al, 1975).

There is an impressive body of work showing that elevated levels of glucocorticoids accelerate aging processes (Sapolsky, 1999). Based on these studies, it would seem unlikely that the CR-induced daily elevation of the plasma free corticosterone level is a component of the hormesis pathway leading to life extension in rodents. However, this view ignores the fact that for any given circumstance, there is an optimal level of any hormone, and that either a lower or higher level than the optimal has negative consequences.

HORMESIS HYPOTHESIS NOT FAVORED BY MOST BIOGERONTOLOGISTS

Although the hormesis hypothesis has gained supporters in recent years, it is still not favored by most biogerontologists (Sinclair and Howitz, 2006). In part, this is because most biologists are skeptical of the hormesis concept for a variety of reasons such as the low level of the harmful agent needed to observe hormesis, the often small magnitude of the effect, the difficulty that the concept poses for regulatory agencies, and its association with homeopathic medicine (Calebrese, 2002). Since most biogerontologists were trained and functioned as biologists before focusing on gerontology, they carry the baggage of biology for better or for worse. However, the major reason for the skepticism of biogerontologists is the gerontologic concept of allostatic load, i.e., the cumulative physiological toll over time by the organism's efforts to adapt to stressors (McEwen, 1998). This concept makes them wary of the long-term beneficial effects of stressors. Although clearly allostatic load is an important gerontologic concept, those of us who favor the hormesis hypothesis feel that whether a stressor has pro-aging or anti-aging action depends on both the nature and the intensity of the stressor. Indeed, the hormesis hypothesis predicts the validity of the allostatic load hypothesis.

UNIFYING FRAMEWORK

As discussed in the overview section of this paper, there have been many hypotheses proposed regarding the biological process underlying the life-extending and anti-aging actions of CR. Each of these hypotheses is based on an action of CR, such as attenuation of oxidative stress, decreased body temperature or deceased concentration of plasma insulin. Most of these hypotheses delineate a specific process that is likely to be involved in the anti-aging actions of CR. Indeed, probably many focus on one component of the overall hormetic process. Thus, the hormesis hypothesis embraces many of the other hypotheses and thereby provides a unifying framework.

However, although hormesis embraces many of the proposed mechanisms underlying the anti-aging actions of CR, it is not likely that it encompasses all of them. For example, CR decreases the rate at which reactive oxygen species are generated (Gredilla et al, 2001). Although the augmentation of protective and repair processes are components of hormesis, there is no reason to believe that such is also the case for processes that modulate the generation of damaging agents. As defined by Rattan, hormesis enables the organism to better cope with damaging agents; it is conceivable, but highly unlikely, that this hormetic mechanism also acts to decrease the intensity of the damaging agent.

While there is abundant evidence to support a major role for hormesis in the anti-aging actions of CR, it is imperative to test this hypothesis by studies that include the potential for falsifying it. It has proven to be difficult to design such studies for the following reasons: 1. As just mentioned, hormesis is not likely to be the only process involved in the anti-aging action of CR; 2. Hormesis probably utilizes multiple pathways in activating protective and repair processes.

CONCLUSIONS

Hormesis evolved because it enabled animals in the wild to survive environmental hazards such as brief, unpredictable periods of food shortage. In the laboratory CR paradigm, the anti-aging action of food restriction employs this hormesis process in a sustained fashion. Although the proximate mechanisms in the hormesis process engendered by CR remain to be fully identified, heat shock proteins, enhanced repair processes, and glucocorticoids appear to be involved.

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